Decision Memo for Ocular Photodynamic Therapy with Verteporfin for Macular Degeneration (CAG-00066R)

Decision Summary

The use of ocular photodynamic therapy with verteporfin in treating occult with no classic subfoveal CNV in "wet" AMD is supported by the VIP study. It should be noted that existing coverage policies on laser photocoagulation for any conditions discussed in this memorandum are not affected by this decision.

Therefore, CMS intends to cover OPT with verteporfin for patients with the "wet" form of AMD who have subfoveal occult and no classic CNV lesions as determined by a fluorescein angiogram. Other uses of OPT with verteporfin, as it relates to "wet" and "dry" AMD and not already addressed by CMS, will not be covered. These include the following patients:

- Patients with minimally classic CNV lesions (where the area of classic CNV occupies < 50% of the area of the entire lesion);
- Patients with juxtafoveal or extrafoveal CNV lesion (lesions outside the fovea);
- Patients who are unable to obtain a fluorescein angiogram; and
- Patients with atrophic or "dry" AMD.

It should be noted that OPT with verteporfin for other ocular indications, such as pathologic myopia or the presumed ocular histoplasmosis syndrome, is not addressed in this decision memorandum and continue to be eligible for coverage through individual contractor discretion.

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Decision Memo

TO: Administrative File CAG: 00066R
Ocular Photodynamic Therapy (OPT) with Verteporfin

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SUBJECT: Coverage Decision Memorandum for Ocular Photodynamic Therapy
DATE: October 17, 2001

This memorandum serves five purposes: (1) describes the pathophysiology of age-related macular degeneration (AMD); (2) discusses available treatments and recent developments in the clinical management of AMD; (3) analyzes relevant clinical literature on the use of ocular photodynamic therapy (OPT) with verteporfin; (4) announces our NCDs in response to a request for reconsideration; and (5) delineates the reasons supporting national coverage of OPT with verteporfin for AMD patients with subfoveal occult and no classic choroidal neovascularization (CNV) lesions as determined by a fluorescein angiogram.

I. Clinical Background

Age-related macular degeneration is a common ocular disease that affects the elderly. Indeed, it is the leading cause of legal blindness in Americans over the age of 65. The estimated prevalence of AMD in Americans 75 years of age or older is 7.1%. [1] While the exact etiology of AMD is not well understood, several risk factors in addition to age have been determined. These include family history of AMD, smoking, and light eye color. Recent findings also suggest that low dietary intake of antioxidants may predispose people to AMD.

AMD involves the destruction of normal macular function. In AMD, acellular debris called drusen accumulates within Bruch's membrane. Bruch's membrane, as shown in Figure 1, is the layer between the outer edge of the retina and the choroid. This layer is important because it keeps the blood vessels of the choroid from leaking fluid into the retina.

There are two basic types of AMD: dry and wet. Dry AMD is the most common type, accounting for 90% of all cases. In dry AMD, the accumulation of drusen, and the resulting effect they have on macular function, leads to central vision deterioration. Wet AMD accounts for 10% of cases, and poses a higher risk of severe central vision loss. In wet AMD, breaks in Bruch's membrane allow vessels from the choroid to grow, leak, and bleed into the subretinal space; this is termed choroidal neovascularization. CNV can cause large distortions of the macula, and can progress quickly (over the course of days or weeks), effectively destroying central vision. While AMD is the most common condition associated with CNV, other retinal disorders such as pathologic myopia, presumed ocular histoplasmosis syndrome, angioid streaks, and retinal hamartomas can be complicated by CNV formation. There is no definitive treatment for dry AMD. For patients with wet AMD, laser photocoagulation has been shown to help reduce the incidence of vision loss in some patients.

Patients suspected of having wet AMD generally undergo fluorescein angiography. There are two basic patterns of fluorescein leakage in wet AMD: classic and occult. In pure classic CNV, the choriocapillaris plexuses that are involved can be seen distinctly. In pure occult lesions, the location of the offending vessels is not recognizable. Many CNV lesions are a combination of both occult and classic with a portion showing a defined site of leakage and another portion being obscured. CNV in AMD is further characterized by one of three locations: subfoveal, juxtafoveal and extrafoveal. Subfoveal, as the name implies, is CNV that lies directly below the fovea. Juxtafoveal and extrafoveal CNV lie progressively further away from the fovea (but still within the macula).

Laser photocoagulation has been shown to decrease the loss of vision by 50% in juxtafoveal and extrafoveal CNV. For subfoveal CNV, laser treatment has been shown to have some benefit, mainly in patients with predominantly classic CNV. Laser photocoagulation by itself destroys the retina overlying its area of application. When applied away from the foveal center (i.e., juxtafoveal or extrafoveal) the effect of the laser itself on vision is variable. When applied to the foveal center, as in cases of subfoveal CNV, the laser is almost assured to destroy some central vision. In addition, subfoveal CNV recurs approximately 50% of the time after "successful" laser therapy. Thus, while laser photocoagulation of subfoveal CNV is preferable to allowing the disease to progress naturally, it is not without significant limitations.

Ocular Photodynamic Therapy (OPT) with Verteporfin: OPT for the treatment of CNV involves the intravenous injection of a photosensitive drug, verteporfin. A laser, which emits light only at verteporfin's absorption peak of 689 nm, is then shined into the eye. It is thought that the excitation of verteporfin generates singlet oxygen and other reactive intermediates that result in temporary closure of leaking blood vessels. The laser is non-thermal; thus it does not produce a heat effect on the retina and causes no damage to the retinal tissue. Verteporfin therapy, however, is not permanent. The closure of leaking blood vessels caused by OPT is often temporary, and these vessels may re-open. Additional OPT treatments, therefore, may be needed.

II. History of Medicare's Coverage on OPT with Verteporfin and Timeline of Recent Activities

Food and Drug Administration (FDA) Status: On April 12, 2000, the FDA approved the use of verteporfin in AMD-related subfoveal CNV in which _ 50% of the lesion is classic (as determined on fluorescein angiogram). On August 22, 2001, the FDA approved verteporfin for the treatment of predominantly classic subfoveal CNV related to pathologic myopia as well as ocular histoplasmosis.

Current Medicare Policy of OPT with Verteporfin: On November 8, 2000, the Centers for Medicare and Medicaid Services (CMS) issued a decision memorandum on the use of OPT with verteporfin for the treatment of AMD. In this memorandum, CMS concluded that this therapy would be covered for AMD patients with subfoveal CNV in whom ≥50% of the lesion was classic on fluorescein angiogram. This decision was based on data from the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) Study Group, a multi -center, and randomized controlled clinical trial. This decision memorandum can be found at http://www.cms.hhs.gov/coverage/8b3-ee5.asp.

Recent Activities: On May 21, 2001, Dr. Kirk H. Packo, president of The Vitreous Society, submitted a formal request for reconsideration of coverage for OPT with verteporfin in the treatment of AMD with occult but no classic CNV. This request was initiated after new evidence became available in May 2001 which suggested that OPT with verteporfin produced a benefit in such patients.

III. Summary of Evidence

Medical Literature

CMS's analysis of the scientific evidence supporting the use of verteporfin with OPT in the aforementioned group of patients concentrated primarily on one study - the Verteporfin in Photodynamic Therapy Study Group (VIP) trial. Reports from two prior studies, The Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group (TAP) reports 1 and 2 were also consulted.[2] [3] The TAP 1 and 2 reports formed the basis of the national coverage determination on OPT with verteporfin which was issued in November 2000. The TAP trial preceded the VIP trial, and the two studies had similar designs and outcome measures.[4] The TAP trial primarily looked at patients in whom the CNV was predominantly classic in nature, while the VIP trial concentrated on patients with occult CNV. For this coverage determination, only the VIP trial results will be summarized.[5]

The VIP study was a double-masked, placebo-controlled, randomized, multi-center clinical trial involving 339 patients from 28 clinical centers in North America and Europe. The study's purpose was to determine if OPT with verteporfin could safely reduce the rate of vision loss in patients with AMD-associated subfoveal CNV. The VIP study group looked at two patient groups: (1) those judged to have occult but no classic CNV on fluorescein angiogram; and, (2) patients with presumed early-onset classic CNV with baseline visual acuity of 20/40 or better. Since the coverage request addressed only the use of OPT with verteporfin for AMD patients with occult but no classic CNV, data summarization will focus on that part of the VIP study that looked at purely occult lesions.

- Inclusion criteria for the VIP study were:
- subfoveal CNV;
- area of the CNV at least 50% of the area of the total neovascular lesion;
- greatest linear dimension $\leq$5400 microns;
- presumed recent progression of disease;
- best-corrected visual acuity at baseline of 20/100 or better; and
- ability and willingness to provide written informed consent.

Patients were randomized to either the verteporfin treatment group or the placebo group. Patients in the verteporfin group received an intravenous injection of 6mg/m^2 body surface area of verteporfin in 30 cc of 5% Dextrose over 10 minutes. The placebo group received 30 cc of 5% Dextrose intravenously over 10 minutes. Fifteen minutes after the start of the infusion, the patient's eye was exposed to a 689 nm wavelength nonthermal laser for 83 seconds. All patients were scheduled for regular three-month follow-up visits. At each regularly scheduled exam, the patients' vision was tested, a dilated fundus exam was performed, and a fluorescein angiogram done. If there was any leakage seen on the fluorescein angiogram, the patient was retreated with the same agent with which they were randomized. Patients were followed for 24 months. To account for missing data points a "last observation carried forward" approach was used in the data analysis. To preserve randomization, guard against patient selection bias, and account for crossovers in the study groups, the authors employed an "intent to treat" analysis.

The authors calculated the necessary sample size with the intent of achieving a power of 90% for the study results. They estimated that 40% of the placebo-treated patients and 20% of the verteporfin-treated patients would have moderate vision loss by the 12- month endpoint. They believed this difference was clinically relevant. To achieve the desired study power, they calculated a necessary sample size of 193 verteporfin-treated patients and 97 placebo-treated patients. A 2:1 randomization (verteporfin:placebo) was done.

A total of 339 eyes in 339 patients were included in this study. Of these, 76%, or 258 eyes, had occult but no classic CNV. Of these 258 eyes, 166 eyes received treatment with verteporfin and 92 eyes received treatment with placebo. The follow-up rates for the 12- and 24-month analyses in these 258 eyes are shown in Table 1.

TABLE 1:Follow-up of the Occult but No Classic Group

Study Group	12 month follow-up	24 month follow-up
Verteporfin group	95% (157/166)	86% (143/166)

Study Group	12 month follow-up	24 month follow-up
Placebo group	90% (83/92)	88% (81/92)

The primary efficacy outcome was the percentage of eyes that suffered moderate vision loss, as compared to baseline, at the 12- and 24-month endpoints. Moderate vision loss was defined as loss of 15 or more letters on a standardized eye chart which corresponds to a loss of approximately three lines of vision from a standard Snellen eye chart. The authors also reported on various secondary outcomes. One of these was severe vision loss, defined as the loss of 30 or more letters from the eye chart (e.g., loss of approximately 6 lines of vision). Other secondary outcomes noted were: mean change from baseline visual acuity, proportion of eyes with visual acuity 20/200 or less, change in the visual contrast sensitivity, and fluorescein angiogram outcome. Fluorescein angiograms were read at a central photograph reading center in a masked fashion.

The VIP study presented statistical significance data on moderate and severe vision loss in patients with occult but no classic CNV only at the 24-month follow-up point. CMS requested the statistical data at the 12-month follow-up point from the investigators. These data demonstrate that at 12 months there was no significant difference in vision loss between the groups. By 24 months, however, the verteporfin group had significantly less moderate and severe vision loss. (Table 2)

TABLE 2:Moderate and Severe Vision Loss at 12 and 24 month Follow-Up

	12 month Follow-up		24 month Follow-up	
	Moderate loss	Severe loss	Moderate loss	Severe loss

	12 month Follow-up		24 month Follow-up	
Verteporfin	51% (84/166)	22% (36/166)	55% (91/166)	29% (48/166)
Placebo	55% (51/92)	33% (30/92)	68% (63/92)	47% (43/92)
	P=0.51	P=0.07	P=0.032	P=0.004

Twenty-seven of the 28 clinical centers measured change in contrast sensitivity (this accounted for 161 verteporfin patients and 90 controls). Starting at three months, the verteporfin group lost less contrast sensitivity than the placebo group. Statistical significance data, however, were only presented for the 24-month follow-up. At 24 months, 20% (32/161) of the verteporfin-treated patients lost at least nine letters in contrast sensitivity vs. 34% (31/90) of the placebo-treated patients (p=0.01).

Fluorescein angiogram outcomes demonstrated less progression of occult leakage in the verteporfin-treated patients at both the 12- and 24-month milestones, although the difference was significant only at 12 months. Of the verteporfin-treated group, 55% (91/166) had progression of leakage at 12 months as compared to 73% (67/92) in the placebo group (p=0.004). By 24 months, however, the data showed 46% (77/166) of verteporfin patients vs. 57% (52/92) of placebo patients with progression of occult leakage (p=0.12).

The patients with moderate and severe vision loss were further analyzed along the following subgroups: age, gender, systemic hypertension, smoking history, evidence of prior photocoagulation, presence of blood as a lesion component, visual acuity score, and lesion size. The authors noted that no subgroup was identified in which the placebo-treated eyes fared better than those treated with verteporfin. In terms of both preventing moderate and severe vision loss, each subgroup showed some characteristic that demonstrated an improved outcome with verteporfin. No one subgroup was clearly superior at predicting visual outcome with verteporfin therapy.

As stated earlier, re-treatments were done if there was continued leakage on fluorescein angiogram at each three-month follow-up. The frequency of re-treatments was greatest in the first 12-month period as compared to the second 12-month period for both verteporfin and placebo-treated patients (Table 3).

TABLE 3: Re-treatments at 12 and 24 months

	0-12 months	**13-24 months**
Group	Mean # tx	Mean # tx
Verteporfin	3.1	1.8
Placebo	3.5	2.4

Adverse effects were reported for the entire study population of 339 patients with no reporting on the subgroup of patients with occult but no classic CNV. Overall, a higher number of verteporfin-treated patients reported an adverse effect as compared to placebo-treated patients (42% vs. 23%, no p value given). Common side effects included blurred vision, injection site related problems, and back pain during infusion. The reported adverse effects from verteporfin use noted in this study also occurred at a similar frequency in the TAP trial. In addition, the reported side effects were noted in both the manufacturer drug prescribing information and a review of the National Library of Medicine's MEDLINEplus drug prescribing web site.

Position Statements:

The Vitreous Society, the largest retinal organization in the world, has taken the position that the use of verteporfin for select patients with purely occult CNV is standard of care. It released this opinion on its web site (www.vitreoussociety.org) on February 23, 2001 (three months prior to publication of the VIP study due to pre-publication release of the study's data to the Society). Upon publication of the article, the Vitreous Society also sent a "Special Clinical Alert" to its 1500+ members alerting them to the VIP study's findings. The American Academy of Ophthalmology published a technology assessment in the December 2000 issue of its journal, *Ophthalmology*, but this assessment addressed only the results from the TAP trials (verteporfin use in predominantly classic CNV).

IV. CMS Analysis

The VIP study was well designed with limited potential for unintentional bias. It was double-masked, placebo-controlled, randomized, and included evidence from 28 centers in North America and Europe. There were consistent results across two vision outcome assessments (i.e., visual acuity and contrast sensitivity) as well as confirmatory fluorescein angiographic studies. The authors also reported consistent results across all study centers. Given these consistencies, the treatment benefit seen with verteporfin therapy seems unlikely to be due to chance.

To account for any missing data, the authors used the last recorded observation and carried it forward. This is a potential source of bias that can affect the data either on the side of the treatment or against it depending on what the results of the last observation was. Such bias was minimized by the high follow-up rate: 86% of the verteporfin-treated patients and 88% of the placebo-treated patients completed 24 months of follow-up. The authors reported that an analysis of the data was performed without the last observation carried forward, and that analysis produced similar results. The authors do not report the actual data from this alternative analysis.

The primary and secondary health outcomes measured in the study (e.g., moderate and severe vision loss, loss of contrast sensitivity, fluorescein angiogram outcomes) were appropriate measures of treatment benefit, as they are outcomes that are routinely used in clinical practice. Visual acuity and contrast sensitivity provide objective measures of visual function, and fluorescein angiographic changes are accepted indicators of CNV progression.

Results of visual acuity loss showed there was little benefit at 12 months for the verteporfin group. By 24 months, however, the verteporfin group had significantly less moderate and severe vision loss as compared to the placebo group. The data clearly show that many verteporfin-treated patients still lost vision at 24 months. What is substantial is that this is a treatment for a group of patients in whom there is little alternative, so slight reductions in vision loss can result in clinical relevancy.

A series of subgroup analyses were conducted on the patients with moderate and severe vision loss. The authors stated that two subgroups of patients fared better with verteporfin treatment: those who presented with smaller lesions (i.e., <4 disc areas) and those whose vision at baseline was 20/50 or worse. A closer look at the results revealed that additional subgroups (i.e., age, gender, smoking history, prior photocoagulation, and presence of blood in lesion) also noted a positive verteporfin treatment effect. The authors do not state if within these other subgroups lesion size and initial vision level were also singularly predictive of vision outcome. Thus, one cannot definitively conclude that any of these subgroup categories can be used to select patients for treatment.

This coverage review is based on one published study, which while strong in design, does leave some questions unanswered. There is no data on the benefit of verteporfin treatment beyond 24 months leaving the frequency of necessary treatments, and the total number of treatments needed over the course of a patient's disease unclear. As Table 3 demonstrated, the frequency of treatments decreased in both groups over the 24-month follow-up. Whether this will continue beyond 24 months is unclear.

The decision to treat is based upon demonstrated fluorescein angiogram leakage. The VIP study found that after 24 months, only 19% of the verteporfin-treatment group had absence of leakage. One can predict that treatments beyond 24 months will be necessary. How long treatments must continue, however, is unclear, and CMS will need to monitor this as experience is gained in using this technology.

Closely coupled with the total amount of treatment is the threshold of visual function below which treatment should cease. The authors in their study did not give an indication of when treatment, outside of no further leakage on fluorescein angiogram, should be ceased. In the CMS decision memorandum of November 2000, which addressed verteporfin in predominantly classic CNV, we stated the determination of whether or not there is visual function worth saving should be left to the patient's treating physician. This remains our position.

V. Conclusion

The use of ocular photodynamic therapy with verteporfin in treating occult with no classic subfoveal CNV in "wet" AMD is supported by the VIP study. It should be noted that existing coverage policies on laser photocoagulation for any conditions discussed in this memorandum are not affected by this decision.

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1 Ryan S, *et al.* 1989

2 TAP Report 1, 1999

3 TAP Report 2, 2001

4 For detailed information on the study design of the TAP trial, please see http://www.cms.hhs.gov/coverage/8b3.asp

5 Verteporfin in Photodynamic Therapy Study Group, 2001

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